

Infections with hepatitis A virus or hepatitis B virus account for most cases of acute viral hepatitis, but the cause of chronic hepatitis is a more complicated issue. There is indirect evidence which suggests that HAV infection seldom results in the more severe variants of hepatitis, or chronic hepatitis, but substantiation of this concept must await the development of satisfactory serologic tests. In contrast, HBV is known to produce the entire spectrum of hepatitis, including fulminant hepatitis, CPH, CAGH and cirrhosis.

The histopathologic features of CAGH are usually not difficult to recognize, but it must be borne in mind that the liver has a limited repertoire with respect to the responses it can make to various insults. Thus, the microscopic appearance of CAGH in the liver of a patient in whom HBV infection is known to exist cannot be distinguished from the features seen in patients taking certain drugs (oxyphenisitin, methyldopa), or in patients with lupoid hepatitis which is not thought to be related to HBV.<sup>43</sup> Rarely, other diseases, such as Wilson's disease, can produce the same pathologic changes.

Treatment of acute and chronic hepatitis is frustrating both for physician and for patient because we have not yet found a specific drug which we can direct toward the hepatitis virus. In acute benign viral hepatitis, there is no evidence that dietary manipulations, corticosteroid therapy or even bedrest affect the course of the disease, and we therefore are left with only nonspecific supportive measures to treat patients. For the most severe variants of viral hepatitis, such as submassive collapse and fulminant hepatitis, corticosteroids are widely used despite the lack of convincing evidence of their efficacy. However, our therapeutic approach is on firmer footing when we deal with symptomatic patients with CAGH. Most patients with this problem, termed chronic active liver disease by the Mayo Clinic group, have been shown to respond to long-term prednisone treatment both clinically and pathologically. Azathioprine has also been studied by this group, but this drug does not appear to have a beneficial effect when used without prednisone.<sup>44</sup>

Viral hepatitis is a vexing and complicated problem, and it is one which is growing more complex each year. I hope that my remarks about some current clinical concepts have provided some perspective for this most important disease entity.

## Serology and Epidemiology

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SEROLOGICAL TESTING for hepatitis traces its origin to precipitin reactions in agar gel involving antibody from multiple transfused subjects and antigen found in occasional persons. The antigen (Australia antigen) first was identified by Blumberg<sup>1,45</sup> in patients with leukemia and with Down's syndrome. Prince<sup>46</sup> and Gocke<sup>47</sup> subsequently identified similar antigens in patients with hepatitis; then it was appreciated that all three groups were working with the same system. The antigen was originally called Australia antigen, then hepatitis-associated-antigen, then hepatitis B antigen. Its occurrence in patients with hepatitis has been well documented.<sup>48</sup> More than one type of particle can be identified by electron microscopy. Doctor Fiala referred to the Dane particle<sup>49</sup> in his discussion as the 42 nm particle with a dense core. The antigen measured in ordinary serological tests for hepatitis is a surface antigen with a diameter of 22 nm composed of the coat of the presumed viral particle.<sup>50</sup> This now is known as hepatitis B surface antigen or HBS Ag. The core antigen is known as HBC Ag. Antibodies to the respective antigens are called anti-HBS and anti-HBC. The initials HBV are reserved for hepatitis B virus when it is definitely identified. This may or may not be identical with the Dane particle.

*Subtypes* of HB surface antigen were first described in detail by LeBouvier.<sup>51</sup> These were identified by observing spurring (evidence of partial identity) between different antigen-positive sera on agar gel diffusion. As previously mentioned, it is now generally accepted that there is a common antigen, known as *a* and two mutually exclusive additional antigenic determinants known as *d* and *y*.<sup>52</sup> Additional antigenic determinants known as *w* and *r* also have been described. Thus far all antigen found in the western world has been type *w* whereas *r* has been found in the Far East.<sup>53</sup>

Differences have been found in the geographical distribution of the *d* and *y* subtypes.<sup>54</sup> The *y* subtype predominates in the Mediterranean countries while *d* predominates in the Far East, Africa and South America. There is a mixed distribution

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in the United States and in Europe. Chronic carriers are more likely to be subtype *d* and acute cases are more commonly type *y*. This difference may reflect a relatively recent introduction of type *y*, especially among drug users. The subtypes are of some use epidemiologically, because infections always appear to breed true to the particular subtype of the infecting agent. Thus, all common source outbreaks are of the same subtype. Identification of a new subtype indicates an alternate source of infection. However, this marker is not of great practical value because of the limited number of subtypes. There is no definite clinical difference in the nature of the hepatitis induced by a particular subtype.

As briefly mentioned by Dr. Fiala, recently a newer antigen-antibody system has been described<sup>55</sup> which appears to be serologically and physicochemically distinct from HBS Ag and its subtypes. It has been designated as *e* antigen and *e* antibody. The presence of *e* antigen in the absence of *e* antibody correlated with chronic persistent or chronic aggressive hepatitis. Demonstration of *e* antibody without *e* antigen was found only in healthy blood donors without clinical, laboratory or histological evidence of hepatitis.

### Serologic Methods for Detection of HBs Ag and Anti-HBs Ag

The *immunodiffusion* method is specific but not very sensitive and requires up to three days for optimal sensitivity.<sup>56</sup> Alternate tests have been developed to increase sensitivity and decrease incubation time, especially for the purpose of screening of donor blood samples. These have included a number of tests based on agglutination or precipitation. The most widely used of these tests is *counterelectrophoresis*,<sup>57</sup> which essentially is an agar gel diffusion augmented by passage of a current through the agar so that negatively charged antigen migrates toward the anode and crosses the antibody gamma globulin which migrates slightly toward the cathode. Both speed and sensitivity are increased by this test. *Complement fixation* has proved sensitive and specific for identification of hepatitis antigen.<sup>58</sup>

*Hemagglutination tests*<sup>59</sup> make use of red cells coated with antigen or antibody. In hemagglutination inhibition tests for HBS Ag, cells coated with purified hepatitis antigen are incubated with a fixed amount of antibody and unknown serum.<sup>59</sup> The presence of antigen in the serum inhibits the hemagglutination reaction. Direct hemagglutina-

tion of antigen coated cells has proved highly sensitive for detection of antibody to hepatitis B antigen. Various types of agglutination tests have been devised in which antibody is absorbed onto red blood cells<sup>60</sup> or other particles and hepatitis antigen causes agglutination of the particles.

These tests are relatively sensitive but they are not sensitive enough to detect the minimal known concentration of serum which can transmit hepatitis; in fact, serum diluted more than a thousand-fold greater than the detection limits by complement fixation was capable of transmitting hepatitis in inoculation studies done a number of years ago.<sup>61</sup> This need for more sensitive tests led to the development of several forms of *radioimmunoassay*. The classical radioimmunoassay procedure involves competition between labeled antigen and unlabeled antigen, in standard or unknown solutions for a finite number of antibody binding sites. One early radioimmunoassay for HB Ag used paper chromatoelectrophoresis to separate antibody-bound from free labeled antigen.<sup>62</sup> A significant improvement in the separation system was made by several other groups who used a second antibody to precipitate antigen-antibody complexes.<sup>63,64</sup> This double antibody system has been especially sensitive for identification of antibody.<sup>65</sup>

A variant of radioimmunoassay was developed at Abbott Laboratories and is now used in a number of blood banks and by many investigators.<sup>66</sup> The principle of this assay is somewhat different. Test tubes are coated with antibody to hepatitis B antigen. Serum unknowns or standards are incubated in the coated tubes then washed out. Antigen present in the sample remains bound to the antibody on the wall of the tube. In the next step, labeled antibody is added to the tube; some of this labeled antibody becomes bound to other binding sites on the trapped antigen particles. The tubes are washed again and presence of antigen in the unknown sample is detected as residual radioactivity bound to the tube. This Ausria® test has proved easy to use but a number of laboratories have had problems with false positive reactions.<sup>67-69</sup> If a serum sample contains antibody directed against guinea pig serum, it will bind to the guinea pig anti-HB coating the tube. The other antibody binding site then will bind labeled guinea pig antibody added to the tube and produce a false positive reaction. A new experimental kit has been developed which uses human antibody to coat the tube and is said to produce significantly fewer false positive reactions.

### Usefulness of HB Ag Testing in Blood Banks

Tests for HB antigen have had several clinical applications. The most widely used application has been for screening of blood donors. Several points can be made:

- Antigen positive blood carries a very high hepatitis risk: In approximately 70 percent of recipients of this blood, biochemical evidence of hepatitis will develop.<sup>70</sup>
- The more sensitive tests will identify from two to ten times as many positive units as agar gel diffusion.
- There is some question whether the additional positive units identified by the solid phase radioimmunoassay carry the same high risk of inducing hepatitis; in some cases this may be because of false positive tests.<sup>71</sup>
- The overall incidence of posttransfusion hepatitis has shown a modest but not overwhelming decrease since donor testing has become routine.<sup>71</sup>
- It has been estimated that approximately two thirds of cases of transfusion hepatitis are transmitted by blood that produces negative tests, either because the tests are not sensitive enough or because some other agent is responsible for the infection.<sup>71</sup>
- Antigen testing gives a reasonable indication of the quality of a whole population of blood donors as to hepatitis risk, even if individual units cannot always be identified. That is, donor populations with high rates of positive units also produce higher rates of hepatitis in recipients. In general, blood obtained from commercial blood banks is more likely to produce higher rates of hepatitis in recipients and have a higher rate of antigen-positive units than blood from the Red Cross or other voluntary sources.<sup>72</sup>
- On the other hand, there has been no proven association between transfusion of antibody to hepatitis antigen and development of hepatitis.<sup>73</sup>
- If there is a choice between using all volunteer-donated blood and antigen testing of commercial blood, untested volunteer blood is considerably safer than tested commercial blood.

### Antibody to HBs Ag

Even with highly sensitive radioimmunoassay and hemagglutination tests for hepatitis B antibodies, the pattern of antibody and immunity is not completely defined.<sup>74,75</sup> One reason may be that HB antigen is not the whole virus. Thus, anti-

bodies against the surface antigen may not provide a good indication of the status of immunity or exposure to the virus.

Antibody has been shown to occur regularly after exposure to the MS-2 strain of hepatitis B virus in studies done at Willowbrook Hospital in New York.<sup>76</sup> Other studies done after exposure to live hepatitis B virus at the same institution showed development of antibody in more than 80 percent of patients during the convalescent phase. It should be emphasized that these antibodies usually could not be shown by less sensitive techniques such as agar gel diffusion and complement fixation.

In transfusion hepatitis, the pattern has not been quite as clear. Using sensitive techniques, preexisting antibody can be shown in 10 to 20 percent of patients who receive transfusions. Occasionally in these patients, hepatitis will develop, possibly due to another agent.<sup>77</sup>

### Detection of HBc Ag and Antibody

More recently a test has been developed by a group at the Division of Biologics Standards for detection of antibody to the core antigen.<sup>37</sup> This group purified core antigen obtained from an infected chimpanzee and used the antigen to develop a complement fixation test for anti-core antibody. They were able to demonstrate anti-core antibody during the acute phase of the disease, before demonstration of surface antibody. They also have found persistent anti-core antibody in chronic carriers of HB antigen, suggesting continued stimulation of antibody production by persistence of the virus. In patients who have recovered from hepatitis B infection, the core antibody seems to disappear. Therefore, presence of anti-core antibody appears to be indicator of ongoing or persistent viral replication.<sup>78,79</sup>

### Detection of Hepatitis A Virus

The immune electron microscopic identification of hepatitis A virus particles in stool suspensions also has been used to show antibody to hepatitis A,<sup>2</sup> as previously mentioned by Dr. Fiala. Purification of a suitable amount of hepatitis A antigen should lead to a serological test for hepatitis A antibody. Such a test promises to offer specific identification of patients with infection due to this agent, similar to other tests which use paired acute and convalescent sera for diagnosis of viral illnesses.

## Development of Hepatitis Vaccine

Inoculation studies have shown that experimental infection with either hepatitis A or hepatitis B produces a high degree of immunity to a second inoculation of the same agent within one to two years.<sup>27</sup> However, development of live vaccines will be extremely difficult since neither agent has been cultured successfully and there are no simple animal models in which to test attenuation.<sup>80</sup> The possibility of inducing chronic liver disease is a major theoretical hazard.

Vaccination with killed or inactivated hepatitis B antigen offers more promise in the short run. Krugman and co-workers have shown that brief boiling of infectious serum destroys infectivity but not antigenicity. After immunization with such a preparation, they showed significant resistance to infection with hepatitis B.<sup>27</sup>

A great deal of attention has been given to the possibility of preventing hepatitis with hyperimmune gamma globulin. Krugman showed either prevention or attenuation of hepatitis B infection in inoculated subjects who promptly received gamma globulin with a high titer of HB antibody.<sup>81</sup> Ordinary pooled gamma globulin has not been shown to have significant protective effects in similar studies or in patients receiving blood transfusion.<sup>82</sup> There are few data on the use of hyperimmune anti-HBs Ag.

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## Complications After Peptic Ulcer Surgery

The cardinal sign of malnutrition after surgical operation for peptic ulcer is weight loss. The cause of weight loss is not eating sufficiently. Although a few people have malabsorption after gastric operations, this is a relatively minor problem. The vast majority of people with weight loss after gastric operations do not eat enough—usually out of a fear of provoking post-cibal symptoms.

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